incidence of endoscopically detected gastroduodenal ulceration and tolerability in patients with Rheumatoid Arthritis.

1. STUDY OBJECTIVES (from study 041 text)

The primary objectives of this study were to:

1. Compare the efficacy of celecoxib 200 mg with that of diclofenac SR 75 mg, when administered twice daily for 24 weeks, in treating the signs and symptoms of rheumatoid arthritis;
2. Compare the incidence of gastroduodenal ulceration in patients receiving celecoxib 200 mg BID with that in patients receiving diclofenac SR 75mgBID for 24 weeks, and
3. Evaluate the long term safety of celecoxib 200 mg taken twice daily for 24 weeks.

Secondary Objective

The secondary objective of this study was to determine the impact of celecoxib on patients' health-related quality of life using the SF-36 Health Survey.

2. Study design: APPEARS THIS WAY ON ORIGINAL

This study was longer than any other controlled study and involved the broadest geographic range of patients. Inclusion and exclusion criteria were similar to the North American trials. There were however, several important differences compared to the North American trials. The international composition introduces variability based on different educational backgrounds and endoscopic training. Difference in terminology used in endoscopy reports bears this out. The lack of baseline endoscopy in a patient population that did not exclude recent prior use of NSAIDs introduces a significant uncontrolled variable: particularly for a study that defines endoscopic ulceration as an endpoint. The long duration of the study does not mitigate this issue. This design, however does mimic the likely clinical setting in which such medications are used (no baseline endoscopy). The only endoscopy was performed at study conclusion or early termination. No aspirin or anti-ulcer therapy was allowed. "The occasional" use of antacid for symptomatic relief was allowed. The only information regarding H. pylori infection was serologic.

3. Results APPEARS THIS WAY ON ORIGINAL

i. Demographics: Study groups were comparable for the following relevant parameters: gender, age, race, history of GI intolerance to NSAIDs, GI bleeding , gastroduodenal ulcer, cardiovascular disease. No baseline H.pylori data is available by study design. H. Pylori status based on serology was performed at the end of the study. The ultimate serologic status revealed no meaningful difference between the study groups in terms of H. Pylori status. No data on alcohol and tobacco use is given.

ii. Patient disposition. The calculated study group size was set at approximately 160 each for endoscopic evaluation and 230 each for efficacy based on assumptions described in the protocol. Safety assumptions included an anticipated ulcer rate of 19% in the diclofenac group and a 2-4% ulcer rate in the celecoxib group with a 90% power at 0.05 two- sided test. Since less endoscopic data were assumed necessary only some study centers included endoscopic

evaluation in their protocol. 132 centers in Europe, Israel, New Zealand, Australia, and South Africa participated. Ultimately, however, overenrollment was 42% for efficacy study purposes and 34% for endoscopic purposes. A total of 326 and 329 patients were enrolled into the celecoxib and naproxen groups respectively. A t the reviewing team's request, the sponsor analyzed the data on the initial population size of 460 based on the first 460 enrollees to be sure that no overpowering of the study occurred. The results were not meaningfully different.

ii Serious UGI events

Two patients experienced serious UGI events. Both of these events occurred in the diclofenac group.

(from text study041)
"**Patient No. SK0001-0512** DER 970620-CL412 (Gastric Ulcer) was a 56 year old female with a history of RA. Concomitant medications included methotrexate, propranolol, and magnesium. The patient was enrolled in the study and randomized to the diclofenac SR 75 mg BID group. Treatment with study drug began on 1 April 1997. On 2 June 1997 the patient began to experience epigastric pain and nausea but without vomiting or melena. On 9 June 1997 the patient complained to her rheumatologist of epigastric pain; she also had increased anemia (no documentation supplied). She denied hematemesis and melena. A rectal exam showed no evidence of melena. Tests for occult stool bleeding were not performed. The study medication was stopped on 9 June 1997 and an endoscopy was performed on 12 June 1997, which revealed "great" gastric ulcer (non-bleeding) of 4x4 cm at the posterior wall in the corporal area with a small blood coagulum on the base. The borders were regular (bleeding did not continue in the time of the investigation). No erosions or petechiae were noted and there were no lesions in the antral portion, the duodenum or the pyloric channel. The patient was hospitalized for treatment on 13 June 1997. The patient was withdrawn from the study due to gastric ulcer. The patient subsequently recovered. Review of the case records by the independent GI committee determined this event was a clinically significant GI event. The Investigator considered that the event was probably related to study drug. The Searle Medical Monitor considered the event to be related to study drug."

This patient had been on diclofenac just prior to beginning the study. Doxycycline was in use at the time of withdrawal for unknown reasons. Case report data did reveal a clinically significant fall in hemoglobin (b)(4) This patient had been on diclofenac prior to her study enrollment. This case is indeed considered a clinically significant UGI event.

(from text study 041)
"**Patient No. UK0004-0786** DER 970418- CL225 (Gastritis Hemorrhagic) was 75 year old male with a prior history of RA. Concomitant medications included methotrexate, folic acid, and prednisolone. The patient was enrolled in the study and was randomized to the diclofenac SR 75 mg BID. Treatment with study drug began on 27 January 1997. On 20 February 1997 the patient withdrew from the study because of dyspepsia. At the Final Visit the patient refused to permit endoscopy. On 26 February 1997, 30 days after start of treatment, the patient experienced melena. The following day he was very pale and fainted several times. He underwent an emergency endoscopy by a non-study physician which revealed multiple gastric erosions without ulceration. The rheumatologist broke the code on the medication revealing it to be diclofenac SR and admitted the patient to hospital. The patient received four units of blood in the hospital. The patient was released from hospital on 10 March 1997. The Investigator and the Searle Medical

Monitor both considered the event to be probably related to study drug. Review of the case records by the independent GI committee determined this event was a clinically significant GI bleeding event."

This patient had been on Indomethacin suppositories up until initiation of the study. He withdrew for dyspepsia 6 days before the development of his clinically relevant adverse event occurred. In addition, the lack of baseline endoscopy makes it impossible to know the time course of the development of his ulcer. The Indomethacin used may well have played a role in the development of this ulcer. It is unknown what medications were taken after discontinuation from the study, if any. Based on the predetermined definition of endoscopic evaluability, this case should not be included in the results given the duration of time between withdrawal and clinical event. Despite these protocol violations; for study purposes this reviewer agrees that it should be considered a clinically significant UGI adverse event possibly related to the active comparator.

iv. Endoscopy results

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Data validation:
116 endoscopy reports were reviewed. 4 reports did not specify the number of erosions. The coding staff in some cases chose a category of erosion numbers. This may affect the data on overall gastric score but is unlikely to do so in a meaningful way. No original report form was available on 10 patients. In one case a lesion was described as 1-3mm in size but still considered an ulcer. The definition of an ulcer was a lesion with depth and at least 3mm. in diameter. The coding decision was reasonable but highlights the difficulty in measuring the primary endpoint accurately. In future studies, measuring devices should be used and visual documentation should be considered.

Tables 30 and 31 display the ulcer data for study 041.

Table 30 (from study 041)

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TABLE 31
GASTRODUODENAL ENDOSCOPY RESULTS AT THE FINAL VISIT
PART 2 OF 5: ANALYSIS OF CRUDE ULCER RATE

INTENT-TO-TREAT COHORT (ITT)

	SC-58635 200MG BID (N= 326) (a)	DICLOFENAC 75MG SR BID (N= 329) (a)	p-VALUE (b)
CRUDE ULCER RATE:			<0.001
NO ULCER	204(96%)	185(85%)	
ULCER(c)	8(4%)	33(15%)	
TOTAL (d)	212(100%)	218(100%)	

(a) All randomized patients
(b) Cochran-Mantel-Haenszel test stratified by center (p-value from Row Mean Scores Differ)
(c) Ulcer is defined as an endoscopy score equal to 7
(d) Includes only patients in endoscopy ITT cohort

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Table 31 (from study 041)

TABLE 31
GASTRODUODENAL ENDOSCOPY RESULTS
PART 1 OF 5: NUMBER OF PATIENTS WITH ENDOSCOPY PERFORMED BY TIME INTERVAL

INTENT-TO-TREAT COHORT (ITT)

	SC-58635 200MG BID (N= 326) (a)		DICLOFENAC 75MG SR BID (N= 329) (a)	
STUDY DAYS	NO ULCER	ULCER	NO ULCER	ULCER
WK4 (2-42)	9	1	18	6
WK8 (43-70)	3	0	8	4
WK12 (71-98)	4	0	6	1
WK16 (99-126)	3	0	4	3
WK20 (127-154)	9	0	4	3
WK24 (>=155)	176	7	145	16
TOTAL(b)	204	8	185	33

(a) All randomized patients
(b) Includes only patients in endoscopy ITT cohort

The endoscopy data in tables 30 through 31 reveal a statistically significant difference between the two treatment groups. The difference was present for gastric ulcer rate, duodenal ulcer rate and gastric scores.

H.pylori data follows the North American trials in lack of correlation between gastric or duodenal ulcer rate or endoscopic scores and H. pylori status (based on serology at conclusion of the study). Both groups had higher ulcer rates in the H. pylori positive groups but no statistical significance could be shown with the study size available.

Table 32 (from study 041)

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TABLE 31
GASTRODUODENAL ENDOSCOPY RESULTS AT THE FINAL VISIT
PART 6 OF 5: COMPARISON OF H. PYLORI POSITIVE VS. H. PYLORI NEGATIVE (a)
WITHIN EACH TREATMENT GROUP

INTENT-TO-TREAT COHORT (ITT)

	SC-58635 200MG BID (N= 326) (b)	DICLOFENAC 75MG SR BID (N= 329) (b)
ULCER RATE		
PERCENT PATIENTS WITH ULCER		
FOR H. PYLORI (c):		
POSITIVE	7.5(7/ 93)	21.8(19/ 87)
NEGATIVE	1.0(1/ 97)	10.6(18/106)
POSITIVE - NEGATIVE	6.5	11.8
p-VALUE FOR WITHIN TREATMENT DIFFERENCE (d)	0.139	0.173

(a) Positive (negative) patients should test positive (negative) by serology test
(b) All randomized patients
(c) Includes only patients in endoscopy ITT cohort with known HP status
(d) Cochran-Mantel-Haenszel test stratified by center, performed within each treatment (p-value from Row Mean Scores Differ)

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Corticosteroid usage did not correlate with ulcer prevalence in either group. Stratified data were not supplied for other potential risk factors such as history of cardiovascular disease, gastroduodenal ulcer disease, GI bleeding, or GI NSAID intolerance. The baseline data however did show that the 2 groups were well matched in this regard. Unfortunately no stratification is available for alcohol or tobacco use.

v. Summary:

Study 041 revealed a statistically significant lower in ulcer incidence over a 24 week period in patients treated with celecoxib 200mg bid compared to diclofenac SR 75 mg bid. Two clinically significant UGI events occurred in the diclofenac group compared to no such events in the celecoxib group.

V. Clinically significant UGI adverse events:

The sponsor's definition of clinically significant UGI events is presented on page 9 of this review. The lack of clear definition of the terms coffee ground emesis and melena for usage in clinical trials and the imprecise definition of gastric outlet obstruction is of concern. Two cases were classified as significant events related to bleeding where there was no documentation of hemocult positive stool or emesis and without a fall in hemoglobin or hematocrit. A case of gastric outlet obstruction was included where the clinical presentation was indigestion lasting for 20 days without associated vomiting and the endoscopically visualized description was of a "partial gastric outlet obstruction" when presented in the Integrated Summary of Safety information and without significant obstruction when presented within the results of the individual study 022. The reports are reproduced below.

Patient No. US0004-1070 DER No. 970214-CL465 (Gastric Ulcer; GI hemorrhage) was a 62-year old female with a history of OA, glaucoma, orthopnea, dyspnea on exertion, hypertension, cholecystectomy, hysterectomy, non-insulin dependent diabetes, overweight and persistent cold. She had no history of peptic ulcer disease. The patient was enrolled into the study on 15 January 1997 and randomized to receive naproxen 500 mg BID. After 28 days of treatment, the patient was hospitalized for gastrointestinal tract bleeding after experiencing one episode of coffee-ground-like emesis in the morning and two tarry stools in the previous 24 hours. The patient had also been experiencing weakness and nausea. Endoscopy showed one superficial pyloric ulcer and two superficial stomach ulcers on lesser curvature. No active hemorrhage was seen and hemoglobin and hematocrit remained stable throughout hospitalization. A gastric biopsy for Helicobacter pylori (H. pylori) showed oxyntic gastric mucosa with chronic active gastritis. No H. pylori was noted. Treatment included insertion of a nasogastric tube, intravenous fluids, histamine blockers, bismuth subsalicylate, amoxicillin, metronidazole and famotidine. Other concomitant medications included glyburide, benazepril and hydrochlorothiazide. Study medication was discontinued 27 days after the patient started on study drug and the patient was withdrawn from the study. The patient returned unused study medication and refused the Early Termination visit. The patient recovered and was discharged from the hospital after two days. The patient was scheduled for a follow-up esophagogastroduodenoscopy to be performed two weeks after discharge; however she refused any further follow-up for this event. The Investigator was uncertain of the association of these events with study medication. The Searle Medical Monitor considered these events to be related to study medication. This case was determined by the GI Events Committee as a "Clinically Significant GI Bleeding Event" consisting of an

endoscopically identified lesion (2 gastric ulcers and a pyloric channel ulcer) accompanied by melena and hematemesis.

Patient No. US0341-1280 (Hematocrit Decrease, Duodenitis Erosive, Gastritis Erosive) was a 49year old female with a history of right lung emphysema and osteoarthritis. At Baseline, the patient's hematocrit was(b)(4) H. pylori was negative. Endoscopy completed the following day, showed multiple erosions in the antrum with at least(b)(4) bleeding points in the antrum and corpus of the stomach. That same day, the patient was randomized for enrollment and received diclofenac 75 mg BID. The Week 4 endoscopy was performed 22 days later and revealed a(b)(4) hiatal hernia, gastritis in the body and antrum of the stomach and 40-50 petechial lesions in the stomach with one erosion measuring(b)(4) and containing a small clot. There were two antral erosions measuring(b)(4) Three shallow, superficial "ulcers",(b)(4) in diameter, were noted in the bulb of the duodenum. No bleeding was noted. According to the endoscopist, these lesions had more depth to them than erosions but they were not deep lesions. The Investigator felt these lesions were actually erosions, and not ulcers, because they had no measurable depth. The hematocrit that day was(b)(4) The patient had no abdominal pain, melena, hematemesis or other symptoms of gastrointestinal bleeding. Stools for guaiac were not obtained. The Week 8 endoscopy, completed 28 days later, was negative except for (b)(4) petechiae. The patient had one episode of indigestion, which she treated with a single dose of calcium carbonate. The Week 12 endoscopy, completed 29 days after previous endoscopy, revealed 10 petechiae in the antrum of the stomach. An(b)(4) AV malformation was also noted in the second portion of the duodenum. CLOtest was negative. Hematocrit that same day was (b)(4) The patient completed the study and no further follow-up was done. Concomitant medications included multivitamins. The patient has recovered. The Investigator was uncertain whether this event was related to study medication. This event was considered a clinically significant GI event by the independent GI events committee.

This case is discussed in the review of study 071.

Patient No. US0002-0335 (Duodenal Ulcer) was an 80 year old female with a history of Meniere's syndrome, tonsilectomy, tooth abscess, rhinorrhea, myopia, scratchy throat, insomnia, stroke, pneumonia, pleurisy, inguinal hernia repair, indigestion, bladder infection, nephritis, foot and hip fractures, synovitis, lumbar and cervical spondylosis, lumbar disc disorder, hip replacement, osteoporosis, osteoarthritis, benign breast nodule (removed), "chemomatrixectomy," onycholysis, seasonal allergies and RA. The patient was randomized to receive naproxen 500 mg BID. After 22 days of treatment, the patient experienced continuous severe indigestion. Maalox was prescribed. Twenty days later, the indigestion continued; therefore, medication was discontinued and the patient was terminated early from the study. Hematocrit at the time of the Early Termination was(b)(4); hematocrit had been(b)(4) at Screening. Endoscopy performed the following ___ (absent from original report) showed a 4 mm by 11 mm ulcer of the duodenal bulb located on the superior wall and a large postbulbar ulcer of the duodenum located on the anterosuperior wall. This ulcer was deep and the CLOtest was negative for H. pylori at the time of endoscopy. Treatment included omeprazole and famotidine. Other concomitant medications included calcium carbonate, alendronate sodium and hydroxyzine embonate. Follow-up upper endoscopy performed 42 days later showed a deformed duodenal bulb with a completely healed medium sized duodenal ulcer located on the anterosuperior wall. No active ulcertations were seen, but scarring of the distal bulb was noted. There was no significant gastric outlet narrowing. CLOtest was again negative. The patient has recovered. The Investigator and the Searle Medical Monitor considered this event to be probably related to

study drug. This event was also determined to be a clinically significant GI adverse event by the GI Events Committee.

In the integrated summary of safety this case is described somewhat differently:

Patient 022-US002-0335 was an 80-year-old female with a history of OA, RA, CVA, indigestion, and osteoporosis. Concomitant medications included calcium carbonate, alendronate, and hydroxyzine. The patient was enrolled in Study 022 and was randomized to naproxen 500 mg BID. After 22 days of treatment, the patient experienced severe indigestion and was treated with Maalox. However, the indigestion continued and 20 days later study medication was discontinued. Endoscopy performed one day after discontinuation revealed a (b)(4) mm ulcer on the superior wall of the duodenal bulb and a large postbulbar ulcer on the anterosuperior wall of the duodenum. This postbulbar ulcer was deep and created a partial gastric outlet obstruction. CLOtest was negative for H. pylori. There was no significant decrease in the patient's hemoglobin or hematocrit. The patient was treated with omeprazole and famotidine. This event was classified as **gastric outlet obstruction**.

The reviewer's evaluation of these three cases change the data regarding clinically relevant UGI events. The endoscopic safety conclusions remain unaffected by this issue. None of the studies in the sponsor's submission defined clinically significant UGI events as an endpoint and therefore this issue does not deflect from the robustness of the safety endpoints defined in this submission. This review however does reinforce the consequences of choosing valuable clinically important endpoints and defining them prospectively and clearly.

Table 33 displays the clinically significant UGI events presented by the sponsor and the reviewer's assessment. This table is derived from controlled studies lasting 6-24 weeks. Dose of Celecoxib ranged from 100-400 mg BID.

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Table 33

	Celecoxib proposed dosages (n=3753	Ibuprofen 800 mg tid (n=346)	Diclofenac 75 mg bid (n=716)	Naproxen 500 mg bid (n=1366)
Sponsor's tabulation	2	1	3	5
Reviewer's tabulation	2	1	2	3

This table is derived from multiple studies, including 4 studies without baseline endoscopies in patients recently on NSAIDs. These events were not defined as study endpoints. The table includes several different active comparators. The small number of events from merged data in each cell along with the flaws in endpoint definition would suggest caution in interpreting this data. A large study designed to define the relative risks of clinically significant UGI events associated with the use of celecoxib compared to NSAIDs is recommended.

VI. Reviewer's overall conclusions:

1. The varied and multiple studies summarized above convincingly showed that celecoxib, used at the proposed dosages of 100 to 200 mg twice a day, was associated with a statistically significantly lower incidence of gastroduodenal ulcers and gastric erosions compared to naproxen 500mg BID in all three pivotal studies reviewed. The one study comparing celecoxib 200mg BID to ibuprofen 800 mg TID revealed robust support for the safety claims related to gastroduodenal lesions.

2. The data comparing celecoxib to diclofenac were inconclusive. There was one study (041) indicating endoscopic safety superiority of celecoxib over diclofenac while a second study (071) showed no significant differences. The study where no differences were shown, however, had a larger evaluable endoscopy cohort and included a baseline, ulcer free endoscopy before randomization. This gave a truer de novo and drug related ulcer incidence than the other study. Furthermore, the multiple interval endoscopies over time, all revealing a lack of statistical difference between the groups, add statistical support to this conclusion. On the other hand, study 041 was a study of longer duration. The ulcer statistics were as expected in the context of the other trials. The 4% ulcer incidence at 4 weeks and 7% final cumulative ulcer rate at 12 weeks in study 071 was within the range of ulcer rates on celecoxib in the other studies over 12-24 weeks. The diclofenac associated ulcer rate of 10% in study 071 was similar to the 11% gastroduodenal ulcer rate previously reported among 175 patients receiving diclofenac 50mg bid to tid in a double blind multicenter study of diclofenac and diclofenac/misoprostol. Baseline and 12 week endoscopy were performed in this study as well. The clinically significant UGI event rates did not differentiate the UGI toxicity of these two drugs either. It is concluded that there are no compelling data to suggest that diclofenac and celecoxib use are associated with statistically significant differences in UGI gastroduodenal ulcer rates at the doses and durations studied.

3. None of the studies in this submission statistically addressed the issue of comparability to placebo. Numerical data in this review did suggest a difference between placebo and celecoxib. Naproxen and ibuprofen in studies 021, 022, 062 and 041 were associated with a (b)(4) % higher incidence of ulcers compared to the placebo groups in studies 021 and 022. Celecoxib was associated with a (b)(4) higher incidence compared to the placebo groups in studies 021 and 022.

4. Interesting information regarding H. pylori infection can be gleaned from these studies. The lack of consistent association between H. pylori and ulcer incidence across all treatment groups is in keeping with the medical literature on this subject. Regardless of the methodology (serology with flexure test, CLO test, histology or concordance of methodologies) no consistent correlation was ~~used~~ seen. The lack of correlation in the placebo group is surprising given the wealth of literature showing an association between H. pylori infection and gastroduodenal ulcer in the absence of other apparent risk factors. The small number of patients in the placebo ulcer group may explain this finding. In addition, the patients studied do not represent a naïve population. They all had previously been on NSAIDs for their arthritic condition. This may well have affected gastric mucosal susceptibility to injury. Adaptation of the gastric mucosa, cytoprotective mechanisms and upregulation of protective mediators may be operational. These poorly defined factors and the relatively small ulcer populations in these studies may also play a role in the results . Finally, a review by Laine in the March 1993 Gastroenterology Clinics of North America on H.pylori and NSAIDs gives a good pathophysiologic and empiric review of this subject and suggest no connection between H. pylori and NSAID related ulcers.[6] Although an

interventional study by Chan published in 1997 strongly supported a connection between H.pylori infection and NSAID related ulcers, the current data along with data presented by Laine appear more compelling.[7]

5. When data from the five pivotal endoscopic studies reviewed were combined, there was a statistically significant ulcerogenic effect of low dose aspirin in the celecoxib group. This rate, however was still lower than the ulcer rate among the NSAID groups. This aspirin effect was not seen with statistical significance in the placebo group. This subgroup however was much smaller than the celecoxib groups combined. It is postulated that there may have been a statistically significant effect of aspirin on ulcer rate in the placebo group had the group size been larger. There was no effect of aspirin in the active NSAID comparators when taken as a whole. It appears counterintuitive that two mucosa-damaging chemicals do not have an additive effect. These results may reflect a biological interaction between aspirin and NSAIDs on the gastroduodenal mucosa. Another plausible explanation is that the NSAIDs alone have a much more powerful effect on the gastric mucosa than the aspirin, obscuring any small additive effect. The data presented from study 022 however seemed striking. In this study 0/16 naproxen treated on aspirin patients developed ulcers compared to 37/194 patients on no aspirin. The marked difference of patients per cell (16 vs 194) makes interpretation of these findings difficult. Although these data appear to suggest a protective effect of aspirin on naproxen related ulcers, an effect supported by statistics, the other studies did not even support this finding as a trend. These trials, however, were not designed to analyze the role of aspirin co-administration and overinterpretation of one data subset would be unwise. It seems valid to conclude that in these studies, aspirin did increase the ulcer risk in celecoxib treated patients and that this increase could be measured. This risk, however, remains lower than the risk of gastroduodenal ulcers associated with the use of naproxen or ibuprofen.

6. The review notes several design flaws including, imprecise data collection methodology and vague endpoint definitions that should be improved in future studies in this area. As outlined in the individual study reviews, simplification of the case report forms and closer adherence by endoscopists to the requirements of the protocol would likely improve the quality of the data collected.

Methodological problems are of concern as well. When size of a lesion is relevant, such as the 3mm lower limit for definition of an ulcer, a standardized form of measurement is recommended. The intra and interobserver variability in distinguishing a 2mm from a 3mm lesion with endoscopic estimation has not been defined and is likely to be large. This methodological problem alone makes it difficult to compare data from this submission to data from the medical literature. Within the submission however, the controlled, randomized and blinded nature of the execution of the study protocols should maintain the integrity of comparative data.

The endpoints of greatest clinical concern when studying the commonly used NSAIDs are the complications of perforation, clinically relevant bleeding, obstruction and death. These events occur with low frequency but because of the high prevalence of the use of NSAIDs the absolute public health risk is high. For this reason, endoscopically proven ulcers have been defined as the surrogate of choice in this submission. Future studies should address the true clinically meaningful endpoints to corroborate the assumption that the development or presence of ulcers correlate with adverse clinical outcomes (and to quantify this relationship if present). Such studies must use clear and relevant endpoints to address this issue. Three out of 11 cases presented by the

sponsor as clinically significant UGI events within their controlled studies and described in the text of this review were not felt to meet reasonable criteria. This lack of standardization of definitions and procedures is of concern for future studies.

The endoscopic data presented in this submission are sufficiently robust and statistically significant, that the methodological problems described do not impact on the conclusions described above.

VII. Recommendations for regulatory action

1. It is recommended that the sponsor be permitted to claim less gastroduodenal lesions associated with celecoxib 100-200 mg bid compared to ibuprofen 800 mg tid or naproxen 500 mg bid. This recommendation is based on the results of studies 021, 022, 071 and 062.

2. It is recommended that the sponsor not be permitted to claim less gastrointestinal injury associated with celecoxib 100-200 mg bid compared to diclofenac 75 mg bid. This recommendation is based on the data from studies 071 and 041.

3. It is recommended that the sponsor not be permitted to make claims regarding comparability to placebo. This recommendation is based on the results of studies 021 and 022 as well as using placebo group data from these studies in analyzing studies 071, 062 and 041.

4. It is recommended that the sponsor not be permitted to make claims regarding superiority in the rates of clinically significant UGI events compared to NSAIDs based on the lack of adequate data.

5. It is recommended that future studies with well defined and clinically important UGI endpoints be planned to address safety claims related to clinically significant UGI endpoints. These studies and post marketing experience will be needed to accurately define the relationship between this new molecular entity and the class of drugs currently in use and described as NSAIDs.

6. It is recommended that future studies include as an objective the evaluation any associated risk with the use of celecoxib in combination with low dose aspirin in the populations likely to be prescribed celecoxib if approved.

/s/ [redacted]

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